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Unique Mosaicism of Tetraploidy and Trisomy 8: Clinical, Cytogenetic, and Molecular Findings in a Live-Born Infant

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We report on a live-born infant with mosaicism of tetraploidy and trisomy 8 who had craniofacial abnormalities, cardiac and genitourinary defects, agenesis of the corpus callosum, and anomalies of limbs. The infant died at age 14 weeks. Molecular studies were done on peripheral blood lymphocytes and cultured amniocytes to determine the origin of the cytogenetic abnormalities. On the basis of the results, we describe a possible mechanism to explain these abnormalities. To our knowledge, this infant represents the first reported case of mosaic trisomy 8 with a tetraploid cell line.

KEY WORDS: trisomy 8, tetraploidy, mosaicism

INTRODUCTION

Trisomy 8 is usually found as a mosaic with a normal cell line. Patients with complete trisomy 8 are rare. We describe a live-born infant with multiple congenital anomalies whose karyotype was 92,XXYY in amniocytes, 47,XY,+8 in cordocentesis and peripheral blood lymphocytes, 47,XY,+8/92,XXYY in skin fibroblasts, and 47,XY,+8/92,XXYY/94,XXYY,+8+8 in the placenta. Based on molecular studies, we describe a mechanism to explain the cytogenetic abnormalities. To our knowledge, our patient represents the first reported case of mosaic trisomy 8 involving a tetraploid cell line.

CLINICAL REPORT

The infant was born to a 28-year-old G_2P_1 mother and 31-year-old father at 38 weeks gestation by normal, spontaneous, vaginal delivery. The mother did not have any illnesses or take any medications during the pregnancy. There was no family history of consanguinity, multiple spontaneous abortions, or congenital malformations. The mother and her sister had vitiligo but were developmentally normal. At 27 weeks an ultrasound study showed a large cyst in the supratentorial region of the brain. An amniocentesis documented tetraploidy (92,XXYY) in all 22 cells examined. Because of the abnormal ultrasound findings of hydrocephaly and not microcephaly, as seen in most tetraploids, a cordocentesis was performed showing trisomy 8 (47,XY,+8) in each of 30 cells.

The infant's birth weight was 2,430 g (5th centile), length was 50 cm (25–50th centile), and OFC was 33.5 cm (10–25th centile), and he had multiple congenital anomalies (Fig. 1). Craniofacial abnormalities included enlarged posterior fontanelle (3 × 10 cm), laterally displaced hair whorl, long forehead, deeply-set eyes with downward slant of the lateral aspect of the eyebrows, wide nasal bridge, prominent nares, low-set but well-formed ears, thick lower lip, high arched palate, and micrognathia. Other abnormalities included a long trunk with widely-spaced nipples, ventriculoseptal defect, atrioseptal defect, narrow chest and pelvis, distal hypospadias, grade III left vesicoureteral reflux, long digits with camptodactyly of the second through fifth fingers, mild elbow contractures, and deep creases of the palms and soles (Fig. 2). Multiple attempts at dermal printing were unsuccessful; therefore, dermatoglyphics are not available. Chest roentgenographs showed cardiomegaly, narrow thoracic cage, and 13 pairs of ribs on the right. No vertebral anomalies were identified. Magnetic resonance imaging of the brain showed agenesis of the corpus callosum and a large interhemispheric cyst (Fig. 3).

The patient was discharged from the hospital after 6 days taking digoxin, furosemide, cephalexin, and

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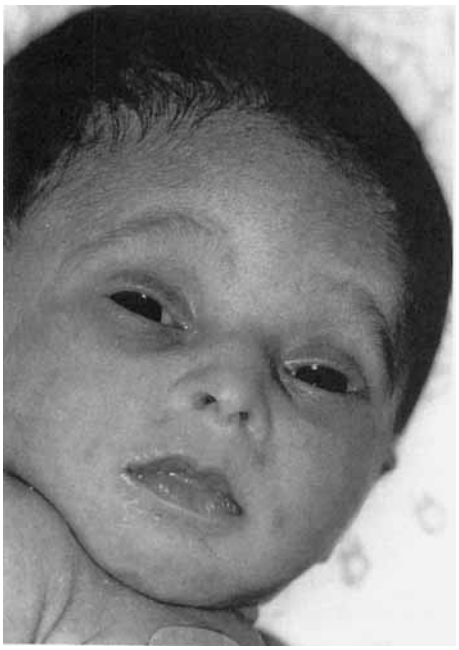

Fig. 1. The patient at birth.

Fig. 3. A parasagittal image of the left calvarium demonstrating agenesis of the corpus callosum and a large dorsal interhemispheric cyst.

sodium citrate and citric acid. He gained weight very slowly taking formula and weighed only 2,980 g at age 7 weeks. At this point, a ventriculoperitoneal shunt was placed to relieve increasing hydrocephalus. He was discharged after an uneventful postoperative course. He was readmitted to the hospital at 13 weeks for congestive heart failure. His condition deteriorated progressively, and he died at 14 weeks. The parents refused an autopsy.

CYTOGENETIC STUDIES

Routine chromosome analysis of amniotic fluid by in situ culture methods showed only tetraploid cells analyzed from 20 independent clones from five separate vessels. Follow-up studies obtained by cordocentesis showed all cells to be trisomy 8 (47,XY,+8). At birth, samples of amnion, chorion, placenta, and peripheral blood were taken for cytogenetic analysis. At 6 weeks of age, the infant's skin was biopsied to determine the extent of mosaicism. A summary of the cytogenetic data from the various tissues (Table I) shows that both the tetraploid and the trisomy 8 lines were present in skin, amnion, and placenta. All three areas sampled from the placenta contained a third and linking cell line of 94,XXYY,+8,+8.

Fig. 2. Deep creases of the soles of the feet.

MOLECULAR STUDIES

DNA was extracted from cultured amniocytes and peripheral blood samples of the propositus and both parents and genotyped using microsatellite markers. There was no pure 94,XXYY,+8,+8 line available for DNA extraction, only mosaic lines. The markers were amplified by radioactive polymerase chain reaction (PCR), resolved on a sequencing gel, and visualized by autoradiography [Webber et al., 1989].

Eleven microsatellite markers mapping on 9 autosomes other than chromosome 8 were studied (Table II). One of these loci (D11S54) was uninformative. At five loci, the patient had inherited an allele that was common to both parents, and these were not completely informative. The other five loci clearly showed biparental inheritance. The presence of only one allele from each parent at these loci in the amniotic fluid and blood of the proband makes meiotic errors in the egg or the sperm an unlikely cause of the tetraploidy observed. DNA from amniocytes showed apparently equal inheritance of maternal and paternal alleles, indicating mitotic nondisjunction as the cause of the tetraploidy.

TABLE I. Distribution of Abnormal Karyotypes

Tissue	47,XY,+8 (%)	92,XXYY (%)	94,XXYY,+8,+8 (%)	Total cells studied
Amniotic fluid	0	100	0	22
Cord blood	100	0	0	30
Peripheral blood	100	0	0	50
Skin	6	94	0	64
Placenta				
Cotyledon A	71	22	7	14
Cotyledon B	82	0	18	51
Cotyledon C	62	25	13	53
Amnion	54	46	0	24
Chorion	100	0	0	4

Five microsatellite markers on chromosome 8 were tested to determine the parental origin of the extra copy. Locus D8S278 was uninformative. At locus D8S593, the DNA from the patient's blood showed two copies of one of the two alleles. However, the parental origin of this allele could not be determined because both parents carried this allele (data not shown). At marker D8S256, both parents shared no alleles, and the patient showed biparental inheritance. In addition, the patient's blood DNA showed increased intensity of the paternal allele, indicating the paternal origin of the extra chromosome 8 (Fig. 4).

DISCUSSION

Patients with complete trisomy 8 are rare [Caspersson et al., 1972; Kakati et al., 1973; Jacobsen et al., 1974; Sperber, 1975; Gagliardi et al., 1978; Moerman et al., 1979]. Most of these patients had cytogenetic analysis on only one tissue. It has been suggested that these reports of nonmosaicism may be invalid if other tissues had been studied, and that mosaicism is necessary for survival to birth [Riccardi, 1977; Pai et al., 1979]. Therefore, mosaicism is a critical component for patients with trisomy 8; however, with nearly all previously reported mosaic cases, the second cell line was normal. We present the first mosaic trisomy 8 patient with a tetraploid rather than a normal cell line. He had the typical manifestations of the trisomy 8 syndrome, including agenesis of the corpus callosum, long forehead, deeply-set eyes, wide nasal bridge with prominent nares, thick lower lip, high arched palate, micrognathia, long trunk with widely-spaced nipples, narrow chest and pelvis, extra ribs, cardiac and genitourinary anomalies, camptodactyly, and deep creases of the palms and soles.

Only seven cases of full tetraploidy in live-born infants have been reported [Golbus et al., 1976; Pitt et al., 1981; Scarbrough et al., 1984; Lafer et al., 1988; Pajares et al., 1990]. Few generalizations can be made about the phenotype, but the most common manifestations include low birthweight, severe mental retardation, microcephaly, and craniofacial anomalies. It is possible that the tetraploid cell line was protective in our patient. However, it seems unlikely. Alternatively, a normal cell line could have existed in a tissue that was not sampled.

The most likely explanation for the cytogenetic findings requires three sequential events. The first is pa-

TABLE II. DNA Markers on Peripheral Blood and Cultured Amniocytes: Determination of Parental Origin

Chromosome	Locus	Father (blood)	Mother (blood)	Proband (blood) (47,XY,+8)	Proband (amniotic fluid) (92,XXYY)	Inheritance
1	D1S152	AA	BB	AB	AB	Biparental
5	CSF-1	AC	AB	BC	BC	Biparental
6	D6S311	BC	AC	BC	BC	
7	D7S483	BD	AC	BC	BC	Biparental
8	D8S1110	AB	AA	AA	AA	
8	D8S503	BC	AC	CC	CC	
8	D8S278	AA	AA	AA	AA	
8	D8S593	AB	AB	ABB[a]	AB	
8	D8S256	BC	AA	ABB[b]	AB	Biparental
9	D9S12	AB	BC	AB	AB	
11	TH	AB	AC	AA	AA	
12	PLA2	AC	BC	BC	BC	
13	D13S133	BC	AC	BC	BC	
15	D15S102	BB	AA	AB	AB	Biparental
15	D15S11	BC	AC	AB	AB	Biparental

[a] ABB represents the extra chromosome 8 that carries the B allele, but the parental origin is indeterminate.
[b] ABB represents the extra chromosome 8 that carries the paternal B allele.

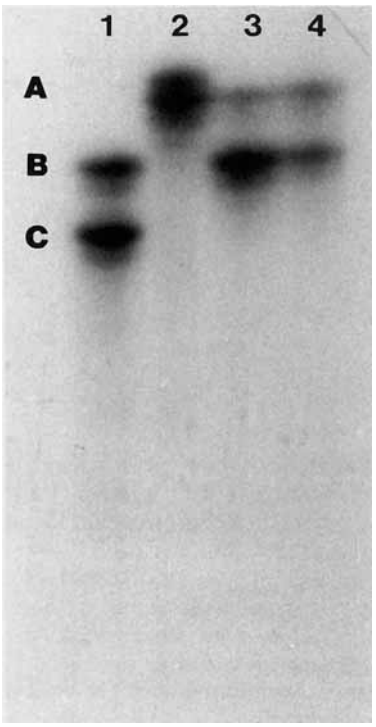

Fig. 4. DNA marker (D8S256) on peripheral blood lymphocytes and amniocytes. **Lane 1**, Father (blood); **lane 2**, Mother (blood); **lane 3**, Proband (blood); **lane 4**, Proband (amniotic fluid). Alleles, A,B,C. In lane 3, the paternal allele (B) was approximately twice as intense as the maternal allele (A), indicating that two copies of the same paternally derived chromosome were present in blood lymphocytes.

ternal nondisjunction of chromosome 8 in the sperm which fertilizes a normal egg and produces a trisomy 8 zygote. A mitotic error then doubles the chromosomes, resulting in the 94,XXYY,+8,+8 line seen in the placenta. Subsequent loss of the extra 8s in this line leads to the tetraploid cell line. This hypothesis is supported by the molecular findings of the paternal origin of the extra 8 and the equal segregation of all alleles in the tetraploid cell line. Another, but less likely explanation for the unusual mosaic karyotype is that the baby was a chimera (i.e., the product of the fusion of twins with two different chromosome abnormalities). However, the finding of the 94,XXYY,+8,+8 cell line in various areas of the placenta excludes this hypothesis.

REFERENCES

Caspersson T, Lindsten J, Zech L, Buckton KE, Price WH (1972): Four patients with trisomy 8 identified by the fluorescence and Giemsa banding techniques. J Med Genet 9:1–7.

Gagliardi ART, Tajara EH, Varella-Garcia M, Moreira LMA (1978): Trisomy 8 syndrome. J Med Genet 15:70–73.

Golbus MS, Bachman R, Wiltse S, Hall BD (1976): Tetraploidy in a liveborn infant. J Med Genet 13:329–332.

Jacobsen P, Mikkelsen M, Rosleff F (1974): The trisomy 8 syndrome: Report of two further cases. Ann Genet 17:87–94.

Kakati S, Nihill M, Sinha AK (1973): An attempt to establish trisomy 8 syndrome. Humangenetik 19:293–300.

Lafer CZ, Neu RL (1988): A liveborn infant with tetraploidy. Am J Med Genet 31:375–378.

Moerman F, Fryns JP, Goddeeris P, Devlieger H, Eggermont E, Lauweryns J, Van Den Berghe H (1979): Complete trisomy 8 in a polymalformed newborn. Acta Paediatr Belg 32:283–285.

Pai GS, Thomas GH, Leonard CO, Ward JC, Valle DL, Pyeritz RE (1979): Syndromes due to chromosomal abnormalities: Partial trisomy 22, interstitial deletion of the long arm of 13, and trisomy 8. Johns Hopkins Med J 145:162–169.

Pajares IL, Delicado A, Diaz de Bustamante A, Pellicer A, Pinel I, Pardo M et al. (1990): Tetraploidy in a liveborn infant. J Med Genet 27:782–783.

Pitt D, Leversha M, Sinfield C, Campbell P, Anderson R, Bryan D et al. (1981): Tetraploidy in a liveborn infant with spina bifida and other anomalies. J Med Genet 18:309–311.

Riccardi VM (1977): Trisomy 8: An international study of 70 patients. New York: Alan R. Liss, Inc., for the National Foundation—March of Dimes. BD:OAS XIII:171–184.

Scarbrough PR, Hersh J, Kukolich MK, Carroll AJ, Finley SC, Hochbergher R, Wilkerson S, Yen FF, Althaus BW (1984): Tetraploidy: A report of three live-born infants. Am J Med Genet 19:29–37.

Sperber MA (1975): Schizophrenia and organic brain syndrome with trisomy 8 (group-C trisomy 8 [47,XX,+8]). Biol Psychiatry 10:27–43.

Webber JL, May PE (1989): Abundant class of human DNA polymorphisms which can be typed using the polymerase chain reaction. Am J Hum Genet 44:388–396.